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Review Article

# Liver disease in pregnancy

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ABSTRACT

Deranged liver function tests are encountered in 3% of pregnancies. The potential causes are classified as those unique to and those just incidental to pregnancy. Pregnancy-related diseases are the most frequent causes of liver dysfunction during pregnancy and exhibit a trimester-specific occurrence during pregnancy. Differentiation of liver dysfunction as that related to and just incidental to pregnancy is the key to management, especially when liver dysfunction is encountered after 28 weeks of pregnancy. It can be judged from the fact that delivery remains the cornerstone of management of pregnancy-related diseases except hyperemesis gravidarum. This is an overview of the causes of liver dysfunction during pregnancy; an update on the underlying mechanisms of their occurrence, especially liver diseases unique to pregnancy; and a methodological approach to their diagnosis and management.


## Introduction

Nearly 3% of pregnancies are complicated by liver disorders. Liver disorders during pregnancy are classified as those related to pregnancy and those just coincidental (occurring during pregnancy or pre-existing). Pregnancy-related disorders are the most common causes of liver dysfunction during pregnancy and are further divided into those associated with or without preeclampsia. Hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy (ICP), preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and acute fatty liver of pregnancy (AFLP) are conditions affecting the liver that are unique to pregnancy. Pregnancy-related liver disorders display characteristic trimester-specific clustering in their occurrence, whereas coincidental liver disorders can occur at any time.

## Physiological changes during pregnancy

*Blood supply* to the liver during pregnancy remains unchanged despite an increase in cardiac output, and so does the liver size. Telangiectasia and palmar erythema, which are otherwise clinical markers of liver disease, are seen commonly during pregnancy (due to a hyperestrogenic state). Decreased *gall bladder* motility with increased secretion of cholesterol in the second and third trimesters increases the lithogeneicity of bile.

### *Liver function tests*

Serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase, and bilirubin values remain unchanged during pregnancy; however, their ranges are changed, with a reduction in the upper end. This is a consequence of hemodilution occurring during pregnancy. Alkaline phosphatase is elevated (up to 300%) but is placental in origin. There is an increase in the hepatic synthesis of coagulation factors VII, VIII, and X and fibrinogen; however, the ranges for prothrombin time and activated partial thromboplastin time remain unchanged. It is believed that prolonged prothrombin time is a good early marker of hepatic synthetic dysfunction. Serum albumin concentrations fall due to hemodilution.

## Hyperemesis gravidarum

HG complicates 0.3–2.0% of pregnancies [1,2]. It is characterized by intractable vomiting in the first trimester (typically 4–10 weeks), leading to dehydration, ketosis, and weight loss of ≥5%, necessitating hospitalization. HG is not a liver disease in the strict sense, but it leads to liver dysfunction in 50% of cases. The mechanism of liver involvement in HG is multifactorial and not well

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understood. Transient hyperthyroidism is seen in 60% of cases [3]. This form of gestational transient thyrotoxicosis is not associated with any unfavorable pregnancy outcome and does not require any treatment. HG-associated liver dysfunction should be a diagnosis of exclusion. A woman presenting with liver dysfunction with or without HG in the first trimester must be carefully investigated to rule out other causes of liver dysfunction (viral hepatitis and drug-induced liver injury).

*Liver function abnormalities*

There are mild to up to 20-fold elevations in AST and ALT (ALT > AST) and rarely mild jaundice. Liver function abnormalities and other biochemical abnormalities resolve upon resolution of vomiting. Other biochemical abnormalities seen are hypokalemia, hyponatremia, and ketonuria.

*Management*

Management of HG is supportive and includes intravenous rehydration with a short period of fasting, followed by reintroduction of a diet rich in carbohydrates and low in fat. Antiemetics such as dopamine antagonists (metoclopramide and domperidone), phenothiazines (chlorpromazine and prochlorperazine), or antihistamine H1 receptor antagonists (cyclizine and promethazine) are used safely during pregnancy [3]. Thiamine supplementation is given with dextrose infusion, particularly in women with a history of prolonged (over weeks) vomiting, to prevent Wernicke's encephalopathy.

## Intrahepatic cholestasis of pregnancy

ICP is the most frequent cause of cholestasis during pregnancy. However, occurrence of cholestasis during pregnancy does not always imply the clinical diagnosis of ICP, because pregnancy itself is a cholestatic condition and chronic liver diseases may be unmasked for the first time during pregnancy with clinical presentation of cholestasis. Differentiation of ICP from other chronic liver diseases is important, because both maternal and fetal prognosis vary. ICP prevalence varies according to countries and populations as there is considerable genetic influence. In European countries, 0.5–1.5% prevalence is seen. South Asia has a higher incidence of ICP.

*Clinical presentation*

Pruritus is the main and most characteristic symptom. Although it is generalized, it might be severe in the palms and soles, and worsens during the night. Pruritus usually develops after 25 weeks, with 80% of cases occurring after 30 weeks. There are no constitutional symptoms. It usually disappears within the first few days after delivery. Jaundice develops in 10% of cases, 2–4 weeks after the development of pruritus, and the bilirubin level is usually <5 mg/dL. Intense cholestasis is associated with steatorrhea, which is usually subclinical but can cause fat-soluble vitamin deficiencies, most notably deficiency of vitamin K. Recent updates point to lysophosphatidic acid, a potent neuronal activator, and autotaxin, the enzyme that forms lysophosphatidic acid, as key elements of the pruritogenic signaling cascade in cholestatic patients suffering from itching [4].

*Liver function tests*

Fasting serum bile acid levels of >10 μmol/L is the key diagnostic test; however, it is not available everywhere. ALT and AST are usually raised 2–10 times but may be elevated up to 20 times. Transaminases are elevated secondary to increased membrane permeability of hepatocytes. Gamma-glutamyl transpeptidase levels are not raised. In fact, raised gamma-glutamyl transpeptidase activity is considered as a marker of chronic liver disease.

*How to make a diagnosis of ICP?*

One should be mindful of the following clinical characteristics when making a diagnosis of ICP:

(1) Typical clinical presentation of pruritus occurring in the second half of pregnancy; a history of itching during a previous pregnancy or use of contraceptive pills lends weightage.
(2) Abnormal liver function tests as described above.
(3) Exclusion of other liver diseases (viral hepatitis and autoimmune liver disease).
(4) A complete recovery of pruritus and liver function tests soon after delivery.

Hence, ICP is a presumptive diagnosis until resolution of symptoms postpartum.

*Pathogenesis*

ICP is associated with abnormal biliary transport across the canalicular membrane, the etiology of which is complex and heterogeneous. Literature suggests that genetic, hormonal, and exogenous factors all play a role in the occurrence of ICP [5].

*Genetic*

Clustering of ICP cases in families and a high incidence in certain ethnic groups suggest a genetic predisposition. Identification of mutations and polymorphism of genes involved in hepatobiliary transport has provided evidence supporting this theory [6,7]. Mutations of the *ABCB4* gene, which encodes multidrug resistance protein 3 (MDR3), as well as those of *ABCB11*, which encodes the bile salt export pump, are likely responsible for about 15% of cases of cholestasis of pregnancy [8–11]. The *MDR3* gene product is a phospholipid flippase that translocates phosphatidylcholine from the inner to the outer leaflet of the canalicular hepatocyte membrane, where it is solubilized by bile acids to form mixed micelles. Other potential gene products of interest include the Farnesoid X receptor and transporting ATPase encoded by ATP8B1 [10,12]. There is, however, no relationship between cholestasis of pregnancy and human leukocyte antigen type.

*Hormonal*

The role of estrogens is supported by the facts that ICP is more common in twin pregnancies (where estrogen levels are higher) and ICP symptoms are sometimes seen in women given exogenous estrogens in the form of contraceptive pills. Abnormalities of progesterone metabolism with an accumulation of sulfate metabolites saturating the hepatobiliary transport system are also implicated in ICP. There are case reports of ICP triggered by a prescription of natural progesterone for preventing preterm delivery in the third trimester [13,14].

*Exogenous*

Had the etiology of ICP been only genetic, all the pregnancies of predisposed women should have been complicated by ICP. However, such is not the case, as ICP recurs only in 60–70% of subsequent pregnancies. This suggests a role of extraneous factors in influencing the occurrence of ICP in genetically predisposed women. Other facts that support the role of exogenous factors are